MTN-038: Extended Duration Tenofovir Vaginal Ring

The study will compare the safety and PK of the Tenofovir (TFV) extended duration intravaginal ring (IVR) to a placebo IVR.

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Phase 1, two-arm, multi-site, randomized (2:1 ratio), placebo-controlled</th>
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<tbody>
<tr>
<td>Participant Follow Up</td>
<td>92 days (91 days of continuous IVR use)</td>
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<td>Study Population</td>
<td>48 healthy, HIV-uninfected women or those assigned female birth, age 18-45 (inclusive)</td>
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<td>Study Sites</td>
<td>Pittsburgh, San Francisco, and Alabama</td>
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Study Rationale

- Safety/tolerability of TFV in vaginal gel and oral tablet formulations demonstrated
- Daily/pericoital TFV vaginal gel not consistently effective for HIV prevention, likely due to low adherence
- While daily oral PrEP found to be protective in some studies, high adherence (6-7 doses/week) needed to protect against vaginal exposures
- Extended duration TFV IVR could overcome adherence/efficacy issues with vaginal gel and daily oral formulations, reduce patient and provider burden
- TFV delivered intravaginally may help prevent HSV-2
- MTN-038 is the first MTN study to evaluate the TFV VR in humans for the intended 90 days of use
  - Potential use for multipurpose technology (e.g. HIV, HSV and pregnancy prevention)
Tenofovir (TFV)/TFV IVR

• Highly potent ARV (NtRTI): inhibits HIV RT enzyme via chain termination, preventing viral replication
• TFV 1% vaginal gel demonstrated to be well tolerated
• Polyurethane reservoir ring containing 1.4 g of TFV, designed to release ~10 mg/day over 90 days
• Target based on trying to achieve sustained PK in the vaginal compartment that matched or exceeded peak PK from TFV 1% gel
Safety of Tenofovir IVR

• Tenofovir IVR found to be safe and well-tolerated in 2 CONRAD studies (128, 130)
• TDF IVR was evaluated in 3 month study of sexually active women
  – 17 ppts enrolled prior to termination (12 TDF, 5 placebo)
  – Among 12 ppts in TDF arm:
    • 2 completed study without complications, 2 had ring removed preemptively
    • 8 ppts in TDF arm developed G1 vaginal/cervical ulceration
      – Occurred average 32 days after ring use (range 23-56 days)
      – 4 were symptomatic, 3 had bilateral ulcers
      – All ulcers resolved after ring removal
  – No ulcerations in placebo arm
• Modifications to MTN-038
  – Added safety visit at day 42
  – Added vaginal and cervical ulceration to ICF Risk section
  – Collection of CVF for biomarkers

CONRAD Tenofovir IVR IB; Keller CROI 2018
Study Visit Schedule

The participant’s menstrual cycle must be considered when scheduling Visit 2- Enrollment (Day 0). Ideally, no bleeding occurs during the first 7 days of product use.
## Study Accrual Target

<table>
<thead>
<tr>
<th>Study-wide Accrual Target</th>
<th>Site Accrual Period</th>
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<tr>
<td>48 participants</td>
<td>6-9 months from site’s first enrollment</td>
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<thead>
<tr>
<th>Site-specific Accrual Target</th>
<th>Pittsburgh</th>
<th>Bridge HIV</th>
<th>UAB</th>
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<tbody>
<tr>
<td>n=24</td>
<td>n=12</td>
<td>n=12</td>
<td></td>
</tr>
<tr>
<td>3-4 participants/month</td>
<td>2-3 participants/month</td>
<td>2-3 participants/month</td>
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Primary Study Objectives

**Pharmacokinetics (PK)**

- Characterize the local and systemic pharmacokinetics of one TFV IVR used continuously for 91 days

- **Endpoints**: TFV levels in plasma, cervicovaginal fluid, rectal fluid, and cervical tissue; TFV-DP levels in cervical tissue

**Safety**

- Evaluation the safety of one TVF IVR used continuously for 91 days.

- **Endpoints**: Grade 2 or higher genitourinary AEs, and Grade 3 or higher AEs
Secondary Study Objectives

**Adherence**
- Evaluate participant adherence to one TFV IVR used continuously for 91 days
- **Endpoint:** Frequency of study IVR removal/expulsions (voluntary and involuntary) and duration without IVR in vagina (by self-report); IVR use initiation and persistence (whether IVR in place at study visits)

**Acceptability**
- Evaluate the overall acceptability of one TFV IVR used continuously for 91 days
- **Endpoint:** Degree to which study participants liked or disliked using the IVR (by self-report)
Exploratory Study Objectives

Vaginal Microenvironment

- Describe the genital microenvironment in HIV-uninfected participants during 91 days of continuous IVR use

- **Endpoints:** Changes in microbiota and biomarkers; impact of microbiota on TFV levels in tissue and plasma

Pharmacodynamics (PD)

- Determine the anti-HIV activity in CVF and cervical tissue, and anti-HSV-2 activity in CVF

- **Endpoint:** Measures of HIV inhibition in CVF and cervical tissue; measures of HSV-2 inhibition in CVF
Exploratory Study Objectives (Cont’d)

**Adherence**

- Evaluate markers of ring use for the TFV IVR

- **Endpoints**: Plasma and CVF TFV levels; residual drug levels in returned IVRs; biomarkers of IVR use

**Acceptability**

- Evaluate components of acceptability of ring use for the TFV IVR

- **Endpoints**: Self-reported attitudes about IVR attributes; interest/preference in a single vs. dual-purpose indication; proportion of participants who find the study IVR to be at least as acceptable as other HIV prevention methods
Key Inclusion Criteria

- Assigned female sex at birth
- Available for all visits and able and willing to comply with all study procedural requirements.
- For the duration of study participation, willing to refrain from inserting any non-study vaginal products or objects into the vagina or rectum starting 24 hours preceding the Enrollment Visit.
- Willing to abstain from receptive vaginal or anal sexual activities for 72 hours prior to each clinical visit and for 72 hours after biopsy collection.
- Willing to use male condoms for penile-vaginal intercourse (PVI) and penile-rectal intercourse for the duration of study participation.
- Per participant report, using an effective, method of contraception 30 days prior to Enrollment and intending to continue the use of an effective method for the duration of study participation.
- Regular menstrual cycles of at least 21 days.
- HIV-uninfected.
Key Exclusion Criteria

• Diagnosed with a **symptomatic UTI or reproductive tract infection (RTI)** or an **acute STI** requiring treatment at Screening or Enrollment

• Clinically apparent **Grade 2 or higher pelvic exam finding**

• Report or evidence of a **gynecologic or genital procedure** 45 days or less prior to Enrollment.

• Use of **Post-exposure prophylaxis (PEP) for HIV exposure and/or Pre-exposure prophylaxis (PrEP)** for HIV prevention within the 3 months prior to Enrollment

• Currently **breastfeeding or pregnant** or planning to become pregnant or breastfeed during the study period

• **Abnormal laboratory results** for ALT, AST, hemoglobin, creatinine clearance, or a positive Hepatitis B surface antigen result